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Avascular Necrosis and Immunosuppression; A Management Dilemma

Fakhriya Alalawi[1,2], Hind Alnour[1,2], Mohsen El Kosi[2,3], Jon Kim Jin[2,4], Ajay Sharma[2,5] and Ahmed Halawa[*2,6]

[1]Department of Nephrology, Dubai Health Authority, Dubai, UAE

[2]Faculty of Health and Science, University of Liverpool, Institute of Learning and Teaching, School of Medicine, Liverpool - United Kingdom

[3]Doncaster Royal infirmary, Doncaster, UK

[4]Nottingham Children Hospital, Nottingham, UK

[5]Royal Liverpool University Hospital, Liverpool, UK

[6]Sheffield Teaching Hospitals, Herries Road, Sheffield-United Kingdom

Corresponding Author: Mr Ahmed Halawa, Consultant Transplant Surgeon, Sheffield Teaching Hospital, United Kingdom, Tel: 447787542128, E-mail: Ahmed.Halawa@sth.nhs.uk

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Abstract

Despite of the fact that renal transplantation may improves the bone metabolic changes associated with end stage renal disease, yet osteoporosis and avascular osteonecrosis remain the most widely recognized osseous complications following transplantation. Head of femur is the most frequent site affected by AVN. The incidence and severity of post-transplant osseous complications is determined by underlying altered physiology such as renal hyperparathyroidism, physical inactivity, adynamic bone disease, vitamin D deficiency, hypercalcaemia, hypophosphataemia, hypomagnesaemia as well as on the type, dose and duration of immunosuppressive medications. Steroids are the major cause of osteonecrosis and osteoporosis, though other immunosuppressive medications such as calcineurin inhibitors, sirolimus and azathioprine have been shown to increase overall bone turnover leading to loss of bone density. A judicious use of steroids-avoiding immunosuppressive protocols can be beneficial; however, this approach might pose a considerable risk of allograft loss due to acute rejection and development of chronic allograft nephropathy especially if the steroid withdrawal is implemented in initial 3-6 months post-transplantation in those patients who are at a higher likelihood of developing immunological failure. Induction by cell depleting agents might help to achieve steroid-free immunosuppressive regimen in such patients.

Keywords: Avascular necrosis; ESRD; Transplantation; Steroids; Immunosuppression

Introduction

Avascular necrosis (AVN) is a pathological phenomenon that evolves as a consequence of vascular disruption to the bone, leading to cell necrosis (of marrow cells, osteocytes and trabecular cells) resulting in with collapse of the bone at its necrotic segment.

Although a successful renal transplantation results in improvement in bone and mineral metabolism associated with end stage renal failure, yet osteoporosis and avascular osteonecrosis remain the most widely recognized osseous complications following transplantation. The head of femur is the most frequent site to get affected. It results in disfigurement of hip joint and, thereby, seriously affecting quality of life, particularly in younger populace between 20 to 50 years of age [1,2].

Incidence

AVN is varied in different literatures; based on participant's numbers, e.g. Kubo had reported osteonecrosis of femoral head in MRI of 25% of 51 renal graft patients; while Lopez-Ben had described similar findings in 4% of 48 recipients. In Lee study, AVN occurred in 6.3% of the 237 recipients and 4.9% of the 473 femoral heads at 8 and 16 months post renal transplant [2-5]. The mean time for AVN diagnosis is 3.5 years post-transplant (ranging from 0.5 to13 years) [3].

Pathogenesis

Nearly 28–88% of graft recipients experience accelerated reduction of bone mass particularly at first year following transplantation, thereafter, the rate declines gradually to 1.7% per year by 10th year post renal-transplantation. Such condition emerges from a reduction in bone mineralization combined with diminishment in bone development [6]. Steroids are the major participant to both osteonecrosis and osteoporosis amongst renal-transplant recipients. Tang et al

had correlated AVN with the cumulative steroids dosage in the first year post renal-transplant, however, other authors concludes no correlations between steroids dose and AVN [3,6-9].

The mechanism by which steroid can induce post-transplant AVN appears to be multifactorial. It includes induction of hypercoagulable status with thrombus formation (as noticed in recipient's plasma at 3 months post-steroid therapy), leading to arterial flow reduction with increase in venous out-flow resistance, particularly intra-osseous vascular flow at femoral head. Additionally, steroids can reduce intestinal calcium absorption and increases its excretion through kidneys, triggering femoral osteoporosis, also it influences PTH secretion (directly and indirectly), changes bone protein matrix, increases osteoclast activities and decreases protein production. Furthermore, the steroids lead to metabolic disorders such as fat embolism of femoral head, rise of intra-osseous pressure with subsequent blood flow reduction, degenerative changes of the hip capsule (have been found in renal transplant of cadaveric donors with intimal wall thickening and sub-chondral bone infarcts) [3]. Dose reduction or early steroids withdrawal is the only and effective way to prevent AVN.

Cyclosporine can influence post-transplant osteoporosis in experimental animals. However, in clinical practice cyclosporine affects bones especially if there is concomitant treatment with steroids [6,10]. Besides glucocorticoid therapy and cyclosporine, other immunosuppressive medications like tacrolimus, sirolimus and azathioprine do have pleiotropic impact by increasing overall bone turnover and to accelerate bone loss. Conversely, mycophenolate mofetil (MMF) seem to be neutral in this respect [6,10].

Other risk factors that have been reported to influence the incidence of AV are: duration on dialysis, type of donor, recurrent rejections, age of the recipients (≤ 40years is a risk factor for AVN), African American race, peritoneal dialysis, previous transplants and postoperative weight gain [3,11]. However, other investigators demonstrated no significant effect of the above-mentioned risk factors on the process of AVN [2].

Clinical presentation of AVN

Localised pain over the affected joint are often the presenting symptom of AVN, regardless of the location, however, at early disease AVN might be painless with nonspecific signs. In instances of AVN of the femur, the pain is frequently confined to the groin region, though it might show in the ipsilateral buttock, greater trochanteric area or even the knee. As the disease advances, the pain may present at rest and excruciating manifestations are usually exacerbated with weight bearing movements like standing & walking, yet are eased by rest. The pain might be extreme, throbbing, deep and often intermittent, get worse by coughing and at night (40% of patients might have night pain concomitant with morning stiffness) [1-3].

Physically there will be a distinctive confinement of passive range of hip movements, mainly in flexion, abduction and internal rotation, particularly after femoral head collapse. As the disease advances, the hip can become stiffer and patient may walk with a limp. A click might be heard when the patient ascents from a sitting position or on external rotation of an abducted hip.

The Trendelenburg sign might be positive in most symptomatic cases. Passive internal and external rotation of the extended leg ("log roll test") may evoke pain consistent with an active capsular synovitis [1-3].

Results and Discussion

Diagnostic procedures

Routine laboratory tests are of no or little value in the diagnosis of AVN; hence the diagnosis is suggested clinically and confirmed with imaging. Plain radiographic evidences of AVN might appear when the disease is at advanced stage. Early radiographic findings in femoral head AVN include femoral head lucency and subchondral sclerosis. With disease progression, subchondral collapse (i.e. crescent sign) and femoral head flattening become evident radiographically. Joint space narrowing is the end result of untreated femoral head AVN [1,6-10].

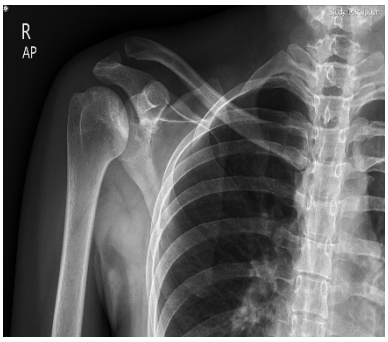

Figure 1: Small areas of sclerosis present at the medial aspect of the humerus, suggestive of avascular necrosis.

(Curtsey: Dr F Alalawi, Department of Nephrology, Dubai Health Authority, Dubai, UAE)

Computed tomography (CT) scanning

CT scans confer significant radiation exposure to the patient and are less sensitive than MRI as a diagnostic modality for AVN.

MRI

Magnetic resonance imaging (MRI) is the best analytic assessment for avascular necrosis and may identify disease as early as 5 days ensuing an ischemic insult, while plain film X-rays and bone scanning might appears normal at early stages [16]. AVN of hip has characteristic MRI findings, and include a

low signal intensity band (seen on T1 and T2 images) that delineates a necrotic anterosuperior femoral head segment. The extent and location of femoral head necrosis on MRIs have been studied as predictors of femoral head collapse. Smaller lesions (less than one fourth the diameter of the femoral head) and more medial lesions (away from primary weight-bearing areas) predict a better outcome [12,13] **(figure 2)**.

99 Technetium bone scan

Abnormalities may appear on a bone scan before they do on plain radiographs, where an osteonecrosis would display as a photopenic area surrounded by increased tracer uptake. Bone scans are considered as less sensitive and less specific than MRI particularly in the earliest stages of the disease, yet the images might be valuable if the utilization of MRI is contraindicated [13].

Positron emission tomography (PET scan)

A few reports have investigated the utility of PET scan as a diagnostic modality of AVN; where the authors had concluded that PET scans have superior diagnostic value in recognizing early stage AVN (Steinberg I) than MRI, SPECT, or bone scanning. However, its use as a routine test is restricted because of its high cost and time-consuming nature [14].

Other diagnostic Procedures

Biopsy, angiography, and measuring bone marrow pressure are invasive measures of confirming the diagnosis of AVN, but these procedures are most useful as investigational modalities [1].

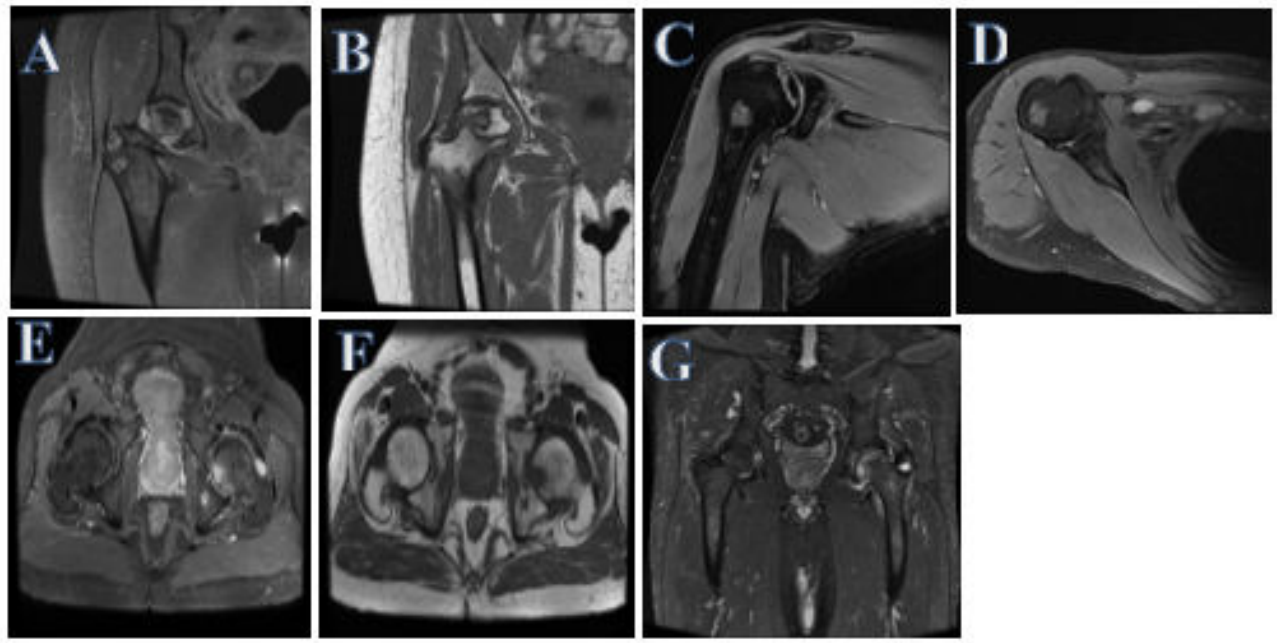

Figure 2: (A,B) Area of avascular necrosis is noted in the MRI of the right femoral head measuring about 3.2 cm in addition to two bone infarcts in the major trochanter of the femur measuring about 1 cm and 9 mm. Mild bone marrow oedema is noted in the right femoral head and proximal femoral bone. **(C,D)** MRI of the right shoulder for the same patient showing Focal area of avascular necrosis in the inner margin of the humeral head. Additionally, multiple enlarged lymph node in the right axilla was noted. **(E-G)** hip MRI of a different patient, showing early avascular necrosis of the left femoral head with flattening, irregularity and a large cyst. Additionally, there is evidence of diffuse osteoarthritic changes involving both hip joints, with decreased joint space on the left side. (Curtsey: Dr F Alalawi, Department of Nephrology, Dubai Health Authority, Dubai, UAE).

There are different staging of the disease based on radiological findings, such as Ficat and Steinberg disease classification systems, Enneking's stages of osteonecrosis, Marcus and Enneking system, Japanese criteria, university of Pennsylvania system and Association of research classification osseous committee (ARCO) classification.

Steinberg staging of avascular necrosis has gained increasing acceptance in the orthopaedic community and it is based on the radiographic appearance and location of lesions. It primarily differs from the other classifications by quantifying the involvement of femoral head which permits direct comparison between series. It is concise and delineates the progression and extent of AVN involvement more precisely.

Seven stages of involvement are identified (see the following table, Table 1). Following staging, the extent of

femoral head involvement is graded as mild, moderate or severe [1,13,15].

Table 1: Steinberg disease classification systems.

Stage I	Normal radiographs; abnormal MRI or bone scan	Stages I-IV are further subdivided according to the percentage of femoral head involvement in to: A, mild (< 15%), B, moderate (15-30%), or C, severe (>30%).
Stage II	Abnormal lucency/ cysts or sclerotic site in femoral head	
Stage III	Subchondral collapse (producing crescent sign) without flattening of femoral head	
Stage IV	Flattening of the femoral head; normal joint space, further graded into Mild: <2 mm Moderate: 2-4 mm Severe: >4 mm	
Stage V	Joint space narrowing, with/ without femoral head (acetabular) involvement	
Stage VI	Advanced degenerative changes	

Management of AVN

Bilateral hip involvement is more typical than unilateral one in post-transplant steroid-induced AVN. Incidence of bilateral involvement might be as high as (>60%) and occult disease in instances of femoral-head AVN warrant imaging of the other leg [3,16]. MRI is the best analytic assessment for avascular necrosis in such cases.

Surgical managements of AVN can be categorized as prophylactic therapy (to retard progression) or reconstruction surgeries (following femoral head collapse) with endoprosthetic replacement.

The most frequently used prophylactic surgical intervention is femoral head core-decompression, to prevent venous congestion and to stimulate repair. Core-decompression is commonly accompanied with bone grafting to improve mechanical support and enhance healing. However, this procedure cannot arrest the progression of the disease. Arthroscopic examination of the joint may show various degrees of chondral flaps, joint degeneration and joint collapse and might help with the brief alleviation of synovitis [1-3].

Reconstruction procedures with total prosthetic hip replacement might be mandatory following hip collapse and can offers pain alleviation in advanced cases of AVN; nevertheless, it might be inadmissible for younger individuals in light of their higher activity levels and limited implants lifespan. Free vascularized fibular grafting showed favourable outcomes and can moderate or arrest the progress of osteonecrosis, enhance revascularization of the bony tissues, prolong symptoms relief and postpone total hip replacement. This method might profit younger recipients with advanced femoral head osteonecrosis and can offer an option technique for conserving femoral head in younger renal-transplant individuals [2,3,6]. Early Intervention has favourable impact on the disease prognosis irrespective of the modality used. Physical treatment offers just symptomatic relief without modifying progression of the disease [1-3,6].

Utilization of autologous stem cells has shown promise in halting the progression of AVN of the femoral head, and subsequently preventing young patients from experiencing total hip arthroplasty [17], however, their use is still within experimental field.

Medical treatment in the post-transplant period

It should incorporate calcium supplements and anti-resorptive medications, such as vitamin D metabolites, bisphosphonates and calcitonin relying upon patient clinical picture [6]. An evidence suggested that calcium with vitamin D derivatives can reduces bone losses and maintains bone mineral density (BMD) at post-transplantation without excessive hypercalcaemia [7,18], moreover, vitamin D deficiency must be treated using similar strategic recommendation for the general public as per KDIGO guidelines. Frank Bienaimé et al had demonstrated that lower 25-hydroxyvitamin-D level at 1year post-transplantation were independently accompanied with a lower GFR and higher risk for interstitial fibrosis and tubular atrophy (P=0.01) with no impact on graft loss or early deaths [19]. Denosumab given subcutaneously twice yearly was shown to increase BMD significantly at total lumbar spine area, total hip and at distal tibia and radius in the first year post renal-transplantation, though it was associated with higher UTI episodes and hypocalcemia [20-22].

There are few data concerning cholesterol-lowering statin therapy to reduce the risk of AVN for those receiving corticosteroids. Given the relatively favourable safety profile of these agents, such treatment ought to be considered [3,6].

Reduction in or early withdrawal of corticosteroid is highly recommended for those patients. There are different ways for glucocorticoids withdrawal in transplant recipients, such as entire steroids withdrawal; which could be early (during the initial 3 to 6 months post-transplant) or late (a year later), complete steroids avoidance (eradicating steroids in the 7th post-transplant day or less) and finally steroids tapered rapidly to 5 mg daily by the 5th post-transplant week with a small maintenance dose thereafter, to reduce acute rejections rate and to evade chronic allograft nephropathy [23,24]. However,

all glucocorticoids avoidance regimens have selected low-risk recipients and utilized aggressive induction therapy.

Avascular necrosis (AVN) and its impact on planning immunosuppressive regimen in renal transplantation

Transplant-recipients with advanced/ or at a high risk of osteoporosis ought to be considered for steroids-avoiding regimens (2D), yet these protocols were associated with high rate of acute rejection and development of chronic allograft nephropathy, specifically if withdrawal were done in the initial 3-6 months post-transplant [23,24]. For patients with advanced bone disease, the benefits might outweigh the risk; however, careful and close monitoring is required. Furthermore, deceased organs convey both a higher rejection risk and allograft loss compared with living donation, owed to ischemic reperfusion insults that had occurred, hence potential candidates with deceased organ source and those with high immunological risk should not be considered for early steroids withdrawal unless the benefits might outweigh any suspected risks.

Intravenous methylprednisolone, in a dose of 0.5-1 gm at the time of vascular anastomosis, is a standard step mainly to reduce inflammatory injury as a result of ischemia-reperfusion. Steroids, if commenced orally should be reduced to low dose by the 3rd to 5th postoperative day [25]. There are a few successful withdrawal protocols to taper steroids gradually in stable patients over 2-4-month time frame. One efficacious regimen is to decrease prednisone dosage by 1mg/day on weekly basis till a daily dose of 5 mg/day is achieved, which is then changed to 10 mg on alternate day, with a weekly lessening of 1mg until the dose is completely tapered off. Another approach is to decrease the dosage every two weeks by 2.5 mg/day till the prednisone dose discontinued totally. Whatever approach is implemented, there is a certain albeit small risk of acute rejection in patients subjected to steroid-withdrawal from small doses of steroids a year post-transplant, hence patient should be made aware of such risk. It is prudent to monitor these patients closely, and if need be, with protocol biopsies [23,24].

The use of aggressive T cell–depleting induction therapy using either anti-thymocyte globulin (ATG) or alemtuzumab seems to facilitate glucocorticoid withdrawal, though data to support this benefit of alemtuzumab use is rather limited. Furthermore, these induction therapies will be beneficial for high immunological risk patients [26]. The maintenance immunosuppression protocol that is clearly showed superior overall graft survival is tacrolimus with MMF [24].

Conclusion

Steroids are the major contributor to both osteonecrosis and osteoporosis among renal-transplant recipients. Nevertheless, other immunosuppressive medications like calcineurin inhibitors, sirolimus and azathioprine might increase overall bone turnover and to accelerate bone loss independently of steroids. Transplant-recipients with advanced bone disease ought to be considered for steroids-avoiding regimens, yet these protocols were associated with higher rate of acute rejection and development of chronic allograft nephropathy, hence careful and close monitoring is required. Moreover, transplant candidates should be aware of all related consequences to transplant surgery; such as the higher risk of osteoporosis and fracture particularly with the potential use of steroids for treating acute rejection episodes. The pros and cons of steroid-free regimen be discussed, but this may not be possible in patients with high immunological risk. Induction by alemtuzumab or ATG might help in achieving steroid-free immunosuppressive regimen in those who are stratified in higher risk group. Transplant teams must endeavour to achieve fine balance of benefits of an immunosuppressive regimen in the light of potential of risks posed to bone and allograft loss due to immunological causes.

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